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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,171	05/04/2006	Ulrike W. Klueh	MTI/101/PC/US	4607

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ALIX YALE & RISTAS LLP
750 MAIN STREET
SUITE 1400
HARTFORD, CT 06103

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
09/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,171	KLUEH ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,9,14-16,19,25,27,28,37-39,51,52,54,59,66 and 68-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,9,14-16,19,25,27,28,37-39,51,52,54,59,66 and 68-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/29/2006;5/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of May 22, 2009, to the non-final action dated February 12, 2009, has been entered. Claims 1, 9, 16, 27, 28, 37, 38, 52, 66, 68, 69, 74 and 75 have been amended, claims 3, 20 and 67 were cancelled and claims 76-78 newly added. Accordingly, claims 1, 2, 4, 9, 14-16, 19, 25, 27, 28, 37-39, 51, 52, 54, 59, 66 and 68-78 remain pending in the application and are under current examination. The claims have been examined commensurate with the elected invention, and the species of the invention.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on May 22, 2009 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner, and indicated as such on Applicants' IDS form.

The reference of Moussy et al. (U.S. Patent No.: 6,497,729) in the IDS submitted on August 26, 2006 has additionally been considered by the Examiner.

Withdrawn Objections to the Specification

The brief description of the figures was objected to in the previous Office action dated February 12, 2009 for failing to refer to the nucleic acid sequence of mouse VEGF by a SEQ ID NO. In view of Applicants' amendment of the specification, the objection is hereby withdrawn.

Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures 37CFR §1.821-1.825

The previous Office action dated February 19, 2009 indicated that the sequence depicted in Figure 22, fails to refer to the sequence by SEQ ID NO, and Applicants are required to provide both a paper and CRF sequence listing in concordance with the sequence depicted in Figure 22.

However, the CRF provided by Applicants is not in ASCII format and thus cannot be entered. Thus, the objection to Figure 22 is maintained.

Withdrawn Claim Rejection - 35 USC § 112- New Matter

Claim 66 was rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement and introducing new matter, in the previous Office action dated February 19, 2009. Applicants have amended the claim to delete the limitation for a subsystem, obviating the ground of rejection. Accordingly, the rejection is hereby withdrawn.

Withdrawn Claim Rejections - 35 USC § 112- Second Paragraph

Claims 9 and 75 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite, in the previous Office action dated February 19, 2009. Applicants have amended the claims to delete the indefinite language, obviating the grounds of rejection. Thus, the rejections are hereby withdrawn.

Maintained & New Claim Rejections - 35 USC § 102

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 1, 2, 4, 9, 14-16, 19, 25, 27, 28, 37, 39, 51, 52, 54, 68, 69, 70, 72 and 73 stand rejected and claims 76-78 are newly rejected under 35 U.S.C. 102(e) as being anticipated by Sayler et al. (U.S. Patent No.: 6,673,596; filed Dec 2, 1999). Applicants' cancellation of claims 3, 20 and 67 renders their rejections moot. The rejection set forth on pp. 6-7 of the previous Office action dated February 19, 2009 is maintained for claims 1, 2, 4, 9, 14-16, 19, 25, 27, 28, 37, 39, 51, 52, 54, 68, 69, 70, 72 and 73 and further applied to new claims 76-78 for reasons of record.

The rejection

The claims encompass an artificial tissue system, comprising a biological matrix configured for contact with an outer surface of an implantable device and a plurality of cells

supported by said matrix, said cells promoting biocompatibility between said implantable device and a biological system.

Sayler et al. teach an *in vivo* biosensor device comprising a genetically engineered bioreporter for detecting glucose, glucagons or insulin target analytes in the body of an animal; the bioreporter device encapsulated on an integrated circuit. Further teaching controlled drug delivery systems capable of being directly or indirectly controlled by the detection device that provide drugs such as insulin to the animal in response to the amount of target analyte present in the body fluids (Title an Abstract; limitation of claims 14, 15 and 68).

Sayler et al. further teach that the monitoring and regulating the level of analytes may be carried out in the tissues and circulatory system of a human (first column, lines 22-24; limitation of claims 9 and 39). The bioreporter preferably comprises a plurality of eukaryotic cells that produce a reporter polypeptide in response to the presence of the target analyte. Exemplary mammalian cells are human cells such as islet β -cell, or immortal stem cells, comprising one or more nucleic acid segments that encode the reporter polypeptide (column 3, lines 54-66; limitation of claims 2, 4, 70, 72 and 73).

Sayler et al. additionally teach that the biosensor may consist of bioengineered living cells entrapped or encapsulated in a polymeric matrix, or in suspension behind a semi-permeable membrane. Examples of matrices include sol-gel or microporous hydrogels (column 23, lines 34-53). Biochips may be coated with Matrigel, a basement membrane material that promotes attachment of epithelial cells. An alternate approach suspends the cells in Matrigel and allows it to form a gel on the surface of the biochip. The cells are then immobilized in the basement membrane material (column 35, lines 42-47; limitation of claims 1, 16, 25, 27, 28, 37, 51, 52, 54, 69 and 75).

Sayler et al. state that post-transplantation host-rejection effects can be minimized through immunoisolation techniques by enclosing non-host cells in hydrogel membranes; and that host ejection of the implanted biosensor is not a an issue if cells from the host are used for the biosensor construction (column 25, lines 14-17 and 26-27; limitation of claims 1 and 19). Further, Sayler et al. teach their implant enclosed in a biocompatible housing (column 17, line 43), that is implanted within the body of the animal, and may be comprised of a polymeric matrix of poly-L-lysine and alginate, and may also further comprise a filter-supported hydrogel

(column 3, lines 40-49). As the matrix, hydrogel and Matrigel are biocompatible and promote cell attachment, they necessarily promote biocompatibility between the implantable device and a biological system (limitation of new claim 78).

Therefore by teaching all the limitations of the claims, Sayler et al. anticipate the instant invention as claimed.

Response to Arguments:

Applicants disagree, arguing that in Sayler the matrix is within the sensor and is part of the sensor, while in the claims of the present application the matrix is in contact with the outer surface of the implantable and the sensor of Sayler does not promote biocompatibility of an implantable device with a biological system, and does not increase the lifespan of the implant device, but instead detects contents of a biological system. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that as indicated in the rejection, Sayler et al. teach that Biochips may be coated with Matrigel, a basement membrane material that promotes attachment of epithelial cells. An alternate approach suspends the cells in Matrigel and allows it to form a gel on the surface of the biochip. The cells are then immobilized in the basement membrane material (column 35, lines 42-47). Thus, it is clear that the basement membrane and cells coat the biochip and are therefore in contact with the outer surface of the implantable device.

With regard to the limitation of the cells promoting biocompatibility, Sayler et al. state: "Host rejection of the implantable biosensor is not an issue if cells from the host are used for the biosensor construction." (column 25, lines 26-27). Therefore using the host's own cells would naturally promote biocompatibility and avoid rejection of the implantable device.

Regarding the increase in lifespan of the device, Sayler et al. teach the same components as instantly claimed, that include a biogel matrix, biological cells and biengineered cells, as well as autologous cells that are refractive to host rejection. Thus, any increased lifespan for the implant device would be a property inherent and necessarily present in the biological matrix and the cellular community contained therein. Sayler et al. additionally teach: "The viability of the devices may be checked by bioluminescence using microfluidics, or by the quantitation of

known standards or other reference solutions to ensure viability and integrity of the system prior to, or after implantation." (column 26, lines 14-17).

Thus, the rejection is maintained for claims 1, 2, 4, 9, 14-16, 19, 25, 27, 28, 37, 39, 51, 52, 54, 68, 69, 70, 72 and 73 and further applied to new claims 76-78 for reasons of record and the preceding commentary.

Maintained Claim Rejections - 35 USC § 103

Claims 28, 37, 38, 59, 66, 70, 71 and 74 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sayler et al. (U.S. Patent No.: 6,673,596; filed Dec 2, 1999), in view of Soykan et al. (U.S. Patent Application Publication 2001/0000802; effective filing date: Dec. 20, 2000). The rejection set forth on pp. 7-10 of the previous Office action dated February 19, 2009 is maintained for reasons of record.

The rejection:

The claims embrace an artificial implant system, comprising an implantable device, a biological matrix configured for contact with an outer surface of said implantable device and a plurality of cells supported by said matrix, wherein the cells induce cellular growth and neovascularization, wherein the implant system further comprises a system for testing the effectiveness of said implant.

Sayler et al. describe an *in vivo* biosensor device comprising a genetically engineered bioreporter for detecting glucose, glucagons or insulin target analytes in the body of an animal; the bioreporter device encapsulated on an integrated circuit. Further teaching controlled drug delivery systems capable of being directly or indirectly controlled by the detection device that provide drugs such as insulin to the animal in response to the amount of target analyte present in the body fluids (Title an Abstract).

Sayler et al. state the bioreporter preferably comprises a plurality of eukaryotic cells that produce a reporter polypeptide in response to the presence of the target analyte. Exemplary mammalian cells are human cells such as islet β-cell, or immortal stem cells, comprising one or more nucleic acid segments that encode the reporter polypeptide (column 3, lines 54-66). Sayler

et al. additionally state that the biosensor may consist of bioengineered living cells entrapped or encapsulated in a polymeric matrix, or in suspension behind a semi-permeable membrane. Further teaching: "The viability of the devices may be checked by bioluminescence using microfluidics, or by the quantitation of known standards or other reference solutions to ensure viability and integrity of the system prior to, or after implantation." (column 26, lines 14-17).

While Sayler et al. do not specifically describe the cells as inducing cellular growth and neovascularization, such was known in the prior art.

Soykan et al. describe an implantable system that includes a carrier and eukaryotic cells, which produce and release a therapeutic agent and a stimulating element for stimulating the release of the therapeutic agent. The system can also include a sensing element for monitoring a physiological condition and triggering the stimulating element to stimulate the delivery device to release the therapeutic agent (Abstract). Soykan et al. state that the drug-eluting cells can be genetically engineered autologous endothelial cells that line the walls of blood vessels, that secrete vasodilatory, thrombolytic or angiogenic factors, such as vascular endothelial growth factor (VEGF), (paragraphs [0031] and [0034], p. 4; paragraph [0042], p. 5; limitation of claims 38, 71 and 74).

Soykan et al. further describe their implant as further comprising a second polymer composition coating at least a portion of the first polymer composition and cells containing a coagulation inhibitory or anti-inflammatory compound (paragraph [0062], pp. 7-8, bridging; limitation of claim 59).

With respect to the implant further configured to test the effectiveness of the artificial tissue system Soykan et al. state that the systems of the present invention include a second implantable device that includes a stimulation element, preferably in contact with a sensing element, and monitors the patient and detects when a stimulus needs to be sent to the cells to trigger release of one or more therapeutic agents (paragraph [0069]; p. 8). As the implant comprises a sensor, the second implantable device constitutes a subsystem sensor that monitors the effectiveness of the implant.

It should be noted that endothelial cells are a component of vascular structures and VEGF is well known for its inherent ability to promote neovascularization, and must necessarily

do so in the biological system.

As stated in MPEP 2112, the express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). Moreover, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference.

"When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). As stated in MPEP 2112: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir.1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

The teachings of Sayler et al. and Soykan et al. are directed to implants and tissue systems comprising genetically altered cells, and means for assessing their viability. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to genetically alter the implanted cells to secrete VEGF to induce cellular growth and neovascularization, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to utilize endothelial cells transformed with a VEGF gene in the implant system of Sayler et al., because such was expressly taught by Soykan et al. to deliver a therapeutic product to a patient.

Response to Arguments:

Applicants disagree, presenting arguments that are substantially the same as those previously stated. Applicants' arguments have been fully considered, but are not found persuasive. Applicants are directed to the response provided above.

With respect to Applicants' argument that new claim 78 requires that the basement membrane itself promote biocompatibility between the implantable device and the biological system, it should be noted that

Sayler et al. teach Matrigel as a basement membrane material that promotes attachment of epithelial cells. Additionally teaching their implant enclosed in a biocompatible housing (column 17, line 43), that is implanted within the body of the animal, and may be comprised of a polymeric matrix of poly-L-lysine and alginate, and may also further comprise a filter-supported hydrogel (column 3, lines 40-49). As the matrix, hydrogel and Matrigel are biocompatible and promote cell attachment, they necessarily promote biocompatibility between the implantable device and a biological system (limitation of new claim 78).

Thus, the rejection is maintained for reasons of record and the preceding remarks.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633